

REMARKS

Claims 1 and 3-9 are pending in the application and have been rejected.

Amendments

Claim 1 has been amended to recite that the first solvent L1 is selected from water or organic solvent. Antecedent basis for this amendment is located at page 3, line 28. Claim 1 has further been amended to recite that the final product is a suspension of nano- or microparticles which contain an active substance embedded in a polymer matrix wherein said active substance is selected from the group of compounds that are sensitive to denaturation, degradation in aqueous solutions or shear forces. Antecedent basis for this amendment is located in the preamble of this claim, and at page 3, lines 17-18 and page 5, lines 13-14.

Claim 7 has been amended to clarify the language of the claim in accordance with the helpful suggestion of the Examiner during the interview.

Interview Summary

Examiner Audet is thanked for courtesies extended in granting an interview with the undersigned, on August 26, 2009. During the interview, the features and advantages of the present invention, the prior art and the present claims were discussed as summarized in the Examiner's Interview Summary Record. Discussion points of the interview are presented and expanded upon below.

Questions Raised in the Interview

Questions were raised during the interview that do not correspond specifically to rejections of record. Answers to these questions are as follows:

A. Solidification of the Polymer

The Examiner inquired as to whether a separate step should be recited for the solidification of the polymer as recited in step b) of the present claims. It is respectfully submitted that no additional step is required, because the solidification of the polymer

occurs as a result of addition of the aqueous surfactant solution, as explained in the present specification at page 4, lines 9-27.

B. Basis for claim 6 as further limiting claim 1.

The Examiner inquired as to whether Claim 6 further limits claim 1 in reciting a specific order of addition of the surfactant solution to the suspension. Variations of this solidification process are described in the present specification at page 4, lines 9-27. The variants include one process whereby the aqueous surfactant solution is added to the suspension of step a), and another process whereby the suspension of step a) is added to the aqueous surfactant solution. Thus, claim 6 does further limit claim 1. As discussed in the interview, "mixing" is generic as to the order of addition of ingredients, and claim 6 designates a specific order of addition, which is a further limitation of the claim.

Claim Rejections – 35 USC §103

Claims 1 and 3-9 have been rejected under 35 U.S.C. 103(a) as being unpatentable over Hutchinson (U.S. Patent No. 5,889,110) in view of Barry et al. (U.S. Patent Application Publication No. 2004/0126900A1), Chen et al. (U.S. Patent No. 7,081,489), Bhagwatwar et al. (U.S. Patent Application Publication No. 2003/0049320) and Yeh et al. (U.S. Patent No. 5,869,103, cited by International Authority in related PCT Search Report).

The present invention provides a method for the preparation of nano- or microparticles, wherein an active substance is embedded in a polymer matrix by precipitating the active substance in a solution containing the polymer, and subsequently solidifying the polymer. The method is different from prior art techniques, because instead of adding the active substance in a solid state to the polymer solution, the active substance particles are formed in situ in the polymer solution by manipulation of solvents. This precipitation and particle formation of the active substance takes place in a solution wherein the polymer is still dissolved in an organic solvent. The polymer is only then

solidified to form the suspension of nano- or microparticles containing the precipitated active substance embedded in a polymer matrix.

As stated in present claim 1, the present invention comprises the steps of:

- a) combining a solution of an active substance dissolved in a smaller amount of a first solvent L1 selected from water or organic solvent with a solution of a polymer in a larger amount of a second organic solvent L2, said solvent L2 dissolving the polymer but being a non-solvent for the active substance, thereby effecting precipitation of the active substance in a solution which comprises the polymer dissolved in an organic solvent to obtain a suspension of the active substance, and
- b) mixing the obtained suspension with an aqueous surfactant solution and solidifying the polymer to obtain a suspension of nano- or microparticles which contain an active substance embedded in a polymer matrix.

Thus, the present claims require solvents L1 and L2 to be mixed together. The mixture of these solvents is a fundamental basis of how the present invention operates. Further, the steps of the process require that the active substance starts in a dissolved state in a solution, and is thereafter always in a liquid. There is never a time when the active substance is dried out until it is safely embedded in a polymer matrix.

This in-situ precipitation by addition of a non-solvent for the active agent to a solution containing both the active agent and the polymer is significant in providing a gentle and efficient precipitation process, and provides advantages that cannot be achieved by the prior art methods. Advantages to the present process whereby the active substance is precipitated in a solution environment without drying are discussed in more detail in the Response filed April 11, 2008 at pages 2-3 of the Response.

In contrast, Hutchinson does not permit mixing of the two solvents discussed in his process, because he freeze-dries the active ingredient and adds it to the second solvent in dry form (Claim 16, step iv).

Hutchinson discloses salts composed of a cation derived from a peptide containing at least one basic group and an anion derived from a carboxy-terminated polyester, processes for the manufacture of such salts, and the use of such salts in the manufacture of

extended release pharmaceutical compositions (i.e. microparticles). See the Abstract. The process of making such microparticles is detailed, for example, in claim 16, which states:

16. Microparticles comprising a composition consisting essentially of a salt formed from a cation derived from a peptide containing one or more basic groups and an anion derived from a carboxy-terminated polyester, which composition has been prepared from at least an approximately stoichiometric equivalent of said polyester carboxylic acid end groups relative to said basic peptide groups, obtainable by a process comprising

i) dissolving the basic peptide and carboxy-terminated polyester in a first solvent in which both the peptide and the polyester are soluble to form a first solution;

ii) freezing said first solution at high speed to form a frozen mixture;

iii) freeze-drying the frozen mixture to remove said first solvent, forming a freeze-dried product;

iv) dispersing the freeze-dried product into a second solvent which is a solvent for the polyester and a non-solvent for the peptide to form a second solution containing said peptide/polyester salt; and

v) removing said second solvent from said second solution by a procedure selected from the group consisting of spray-drying, spray-congealing, evaporation and phase separation coacervation to form a solid product which is in the form of microparticles, or from which said microparticles are thereafter formed.

(emphasis provided)

Note that the first solvent and the second solvent of Hutchinson are never together in the same solution. The first solvent is removed in step iii) before the second solvent is introduced in step iv). In particular, there is no precipitation of the active agent caused by the action of a non-solvent for the active agent (L2), as required by the present claims. Rather, the solidification both in steps iii) and v) is effected via conventional ways of solvent removal. Thus, it is impossible for Hutchinson to carry out an essential step of the presently claimed method.

However, the Office Action at page 4 suggests that due to the “amorphous language” of the present claims “it is still unclear whether the steps of Hutchinson, in

various examples, expressly teach the ‘effecting precipitation’ step as comprising an L1/L2 combination wherein the latter is increased, following a precipitation step, and wherein the L2 is a non-solvent to the goserelin acetate (see e.g. claim 16, step iv).”

First, it is respectfully submitted that this interpretation of Hutchinson to ever have a composition comprising both L1 and L2 is clear error in view of the foregoing. Furthermore, the present claim excludes any drying step (e.g. the freeze drying step of Hutchinson) after formation of the precipitate, because the claims expressly require that the active substance is precipitated “in a solution which comprises the polymer dissolved in an organic solvent to obtain a suspension of the active substance,” and then the obtained suspension is mixed with an aqueous surfactant solution to solidify the polymer. Thus, the claims require a continuity of liquid phase in the system, and no drying is permitted.

Barry et al. describes polymeric nanoparticles functionalized with two or more peptide moieties that possess high affinity to biomolecular targets. The peptide moieties are covalently linked to the nanoparticle polymeric core structure, either directly or via a linker molecule. See the Abstract. Thus, the peptide functionality is on the outside of the particle, and is not encapsulated within a polymer core.

Paragraph [0089] states that it is preferable to functionalize the nanoparticle in an aqueous system. In this process, the residual from the synthesis of the nanoparticle core (surfactants and the oil phase) “can be removed through the use (singularly or in combination) of solvent washing, for instance using ethanol to solubilize the surfactant and oil while precipitating the polymer nanoparticles.” Thus, the nanoparticles are precipitated after being functionalized, and further there is no suggestion that this precipitation actually is the formation of a suspension in which further action is to be taken, as required by the present claims. Barry et al., do not teach or suggest to first precipitate an active agent in situ in a mixed solvent solution to form a suspension, and then to solidify polymer in the suspension to form a suspension of nano- or microparticles containing the precipitated active substance embedded in a polymer matrix.

The Office Action goes on to state that Chen is cited to remedy the deficiency that the combination of references does not teach the precipitation of the active substance prior to solidification. See pages 3- 4 of the Office Action. [Note that only the subject matter

disclosed in the provisional patent application of Chen may be cited against the present application. See the Response filed April 11, 2008 at page 5.]

However, the Chen Patent and the provisional application to which it claims priority both disclose addition of the active substance to the polymer solution in a solid state. Thus, Chen provides no teaching with respect to precipitation of an active substance to form a suspension as set forth in the present claims, and cannot remedy the deficiency identified in the Final Office Action.

The other references of record similarly do not provide a teaching or suggestion of in-situ precipitation of an active agent in a polymer solution prior to its encapsulation in a polymer. Specifically, Bhagwatwar does not contemplate precipitation of the active ingredient, but rather provides delivery of solvated drugs in a gelled polymer droplet-in-oil dispersion. Likewise, Yeh does not contemplate precipitation of the active ingredient. See the discussion of these references at pages 5 and 6 of the Response filed April 11, 2008.

It is respectfully submitted that the present claims are not obvious in view of the foregoing discussion. Even in combination, the references do not teach or suggest to first precipitate an active agent in situ in a mixed solvent solution to form a suspension, and then to solidify polymer in the suspension to form a suspension of nano- or microparticles containing the precipitated active substance embedded in a polymer matrix.

Claim Rejections – 35 USC § 112 2nd

Claims 1 and 3-9 have been rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 has been rejected as being indefinite regarding recitation of L1 and L2 solvents. Claim 1 has been amended to recite that solvent L1 is selected from water or organic solvents, thereby obviating a portion of this rejection. It is respectfully submitted that the claim already clearly identifies that L1 and L2 cannot be the same solvent, because they must have different solubility properties in accordance with the claim. Thus, L1 must be a solvent for the active ingredient, and L2 must not be a solvent for the active ingredient. It is submitted that the skilled artisan can easily screen for such solubility

characteristics, and no further amendment to the claims is required in view of the capabilities of the skilled artisan.

Claim 1 has been rejected as being indefinite regarding recitation of the term "polymer." This term is fully discussed at page 6 of the present specification. It is respectfully submitted that the skilled artisan can readily understand this term in the context of the present specification by reference to the substantial teaching provided therein, and that no further amendment to the claims is required in view of the capabilities of the skilled artisan.

Claim 1 has been rejected as being indefinite regarding recitation of the term "active agent." This term is fully discussed at page 5 of the present specification. It is respectfully submitted that the skilled artisan can readily understand this term in the context of the present specification by reference to the substantial teaching provided therein, and that no further amendment to the claims is required in view of the capabilities of the skilled artisan.

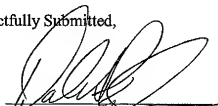
Conclusion

In view of the above amendments and remarks, it is respectfully submitted that the foregoing is fully responsive to the outstanding Office Action. Examination of all claims together, and early favorable consideration and passage of the above application to issue is earnestly solicited. In the event that a phone conference between the Examiner and the Applicant's undersigned attorney would help resolve any issues in the application, the Examiner is invited to contact said attorney at (651) 275-9811.

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Respectfully Submitted,

By:


Dale A. Bjorkman, #33,084
Customer No. 33072
Phone: 651-275-9811
Fax: 651-351-2954